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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Overall 5-yea survival from breast cancer is now 85% and most surviving women are postmenopausal. Nearly half of postmenopausal American women take estrogen replacement to relieve hot flashes and other symptoms of menopause, but this is contraindicated in women with breast cancer. Phytoestrogen supplements can be used as an alternative=, but their effect on the risk of cancer recurrence is unknown. Given the mixed results of phytoestrogen studies regarding breast cell stimulation and inhibition in the medical literature, the effect of phytoestrogen on postmenopausal breast cancer survivors is unclear. To evaluate the effect of a phytoestrogen supplement on steroid hormones and breast epithelial proliferation, 23 disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage 0-11) breast cancer were randomized to either 100mg/d isoflavone tablets or placebo for one year. Hormone levels were measured at baseline, 6months, and one year. Changes in menopausal symptoms and vaginal maturation were also measured.

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Phytoestrogen, Soy, Survivorship

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Modulation of Postmenopausal Steroid Hormone Levels by Phytoestrogens and Correlation with Breast Proliferative Activity and Menopausal Symptoms

Julie R. Gralow, MD

INTRODUCTION:

Overall 5-year survival from breast cancer is now 85%, and most surviving women are postmenopausal. Nearly half of postmenopausal American women take estrogen replacement to relieve hot flashes and other symptoms of menopause, but this is contraindicated in women with breast cancer. Phytoestrogen supplements can be used as an alternative, but their effect on the risk of cancer recurrence is unknown. Given the mixed results of phytoestrogen studies regarding breast cell stimulation and inhibition in the medical literature, the effect of phytoestrogens on postmenopausal breast cancer survivors is unclear. To evaluate the effect of a phytoestrogen supplement on steroid hormones and breast epithlial proliferation, 23 disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer were randomized to either 100mg/d isoflavone tablets or placebo for one year. Hormone levels were measured at baseline, 6 months, and one year. Changes in menopausal symptoms and vaginal maturation were also measured.

BODY:

Task 1: Study Preparation – completed

1. **Development of materials – completed**
   Brochures, flyers, advertisements, web pages, cover letters, as well as data collection forms and study charts were developed. Screening and study data databases were designed and tested for use as well. Both active and placebo tablets were obtained.

2. **Mailings to patients, clinicians, support groups – completed**
   Patients receiving their oncologic care at the Seattle Cancer Care Alliance, and their support groups and care providers were mailed informational materials just prior to when the trial opened to accrual in June 2001. Since then, patients have been approached for recruitment at the time they come in for their clinical follow-up.

Task 2: Subject Recruitment - completed

Screening concluded in October 2003, when 1151 patients had been screened through the Seattle Cancer Care Alliance. We received 78 additional self or clinician referrals. From both groups, 1094 were found to be ineligible, and 112 refused participation. The number one reason for ineligibility at our institution was stage (35%), followed by women who were currently being treated with hormonal therapy (19%). Of the 112 women who refused, the most common reason for nonparticipation was the invasiveness of the breast biopsy (15%) and a refusal to be randomized to isoflavone tablets (8%). Many women, however, declined to give a reason for their refusal.

In an analysis comparing clinic and community based recruitment in the first year of the trial, we found that community based recruitment has yielded more participants. Specifically, 41 eligible women were identified through the clinic over 12 months. However, 80% of those who are currently eligible refused participation. On the other hand, community based recruitment has yielded 25 eligible women over 6 months, and those who were eligible were 15 times more likely to participate. This analysis was presented at the American Institute for Cancer Research meeting last year (see Reportable Outcomes section). This trend continued throughout the trial—by the end of accrual 64% of participants were from community based recruitment, while the remaining 36% were recruited through the clinic.

Task 3: Clinical Trial –completed

Of the 23 subjects randomized, none have reported side effects attributable to the isoflavone tablets. Nineteen have completed the trial, and 4 withdrew before completing therapy per protocol. One Participant withdrew from the trial because of pain associated with breast biopsy. Two withdrew for logistical reasons, and one for personal reasons. Two of the 4 withdrawals yielded evaluable data through 3-6 months of follow-up.

Task 4: Study Follow-up – completed

Study follow-up is completed. The total number of subjects enrolled is 23. Of those; 5 were followed to 24 months, 13 were followed to 12 months, 2 were followed for 6 months, 1 was followed to 3 months, and 2 subjects dropped out of the study.

Task 5: Evaluation of Clinical Materials – 90% complete

1. **Breast Pathology specimens – completed**
   Complete pathology results are available for all subjects. Of the 23 baseline biopsies, 10 were found to have hyperplasia (2 atypical hyperplasia, 8 usual hyperplasia). Immunohistochemical results are available for 18 of 21 baseline biopsies, with the average Ki-67 index of 9.2%. We would expect this to be <5% in a normal risk postmenopausal population. .

   In addition, of the 60 biopsies, all but five had sufficient tissue yield from our ultrasound-guided biopsy method in order to assess epithelial histology and Ki-67 index, as well as mitotic index and ER/PR expression (92% successful yield).

2. **Mammograms – completed**
   We requested 20 baseline films and 29 post-randomization films (17 from the 6-month time point, and 12 from the 12-month time point. Of those, we received 16 baseline, 16 6-month, and 7 12-month film. All 39 films have been digitized and sent for density evaluation. Average baseline mammographic density is 17%, regardless if assessed subjectively by a breast imaging expert radiologist or by computer-assisted software, although the latter has slightly less variance.

3. **Endometrial biopsy specimens – completed**
   All endometrial biopsies have been completed.

4. **Urinary isoflavones levels – completed**

5. **Food frequency questionnaires – completed**
   All questionnaires are completed.

6. **Menopausal symptom questionnaires – completed**
   All questionnaires are completed.

7. **Serum hormone levels – processed, waiting for analysis**
   Blood collections for serum hormone evaluations at baseline, 6 months, and one year are complete. Serum was aliquotted and frozen at –70C within 8 hours of blood collection. These specimens have been transferred to City of Hope. All serum specimens have been processed. Analysis of results is expected this year.

Task 6: Data Analysis and Report Writing – completed

Palomares MR, Gralow JR. The effect of phytoestrogens on normal breast tissue in postmenopausal breast cancer survivors: a feasibility study," poster presentation at the 2002 American Institute for Cancer Research Conference.

Palomares MR, Richardson-Lander A, LaBrash L, Gralow JR. The effect of phytoestrogens on normal breast tissue in postmenopausal breast cancer survivors: an ongoing trial," poster presentation at the 2002 Department of Defense Era of Hope Meeting.

Palomares MR, Goldstein L, Lehman CD, Hopper L, Gralow JR. Feasibility of breast tissue sampling in a chemoprevention trial with histologic biomarker endpoints. *Breast Cancer Research and Treatment,* 82 (Suppl 1): 1034, 2003.

Palomares MR, Hopper L, Goldstein L, Lehman CD, Gralow JR. Acceptability of breast core biopsy as a tissue sampling method for a chemoprevention trial. *Proc Amer Assoc Cancer Res,* 45:1344, 2004.

Palomares MR, Hopper L, Lehman CD, Storer BE, Gralow JR. Effect of phytoestrogens on menopausal symptoms in breast cancer survivors. *Proc Soc Integrative Onc,* 75, 2004.

Palomares MR, Hopper L, Goldstein L, Lehman CD, Storer BE, Gralow JR. Effect of soy isoflavones on breast proliferation in postmenopausal breast cancer survivors. *Breast Cancer Res Treat,* 88 (Suppl 1): 4002, 2004.

Task 7: Additional Studies and Future Directions – in progress

Palomares MR, Goldstein L, Lehman CD, Gralow JR. Acceptability of breast core biopsy as a tissue sampling method for a chemoprevention trial with histologic biomarker endpoints (in preparation).

Palomares MR, Goldstein L, Lehman CD, Storer BE, Gralow JR. A randomized placebo-controled trial of soy isoflavones in postmenopausal breast cancer survivors. (in preparation).

KEY RESEARCH ACCOMPLISHMENTS:

- Conduct of a breast chemoprevention trial with histologic endpoints requiring breast biopsy appears feasible
- Community-based recruitment proved more effective than clinic-based recruitment
- Isoflavone tablets and breast biopsies are well tolerated
- Adequate normal breast tissue for histologic endpoints can be obtained from postmenopausal women >95% of the time using ultrasound-guided core biopsy techniques.

REPORTABLE OUTCOMES:

Palomares MR, Gralow JR. The effect of phytoestrogens on normal breast tissue in postmenopausal breast cancer survivors: a feasibility study," poster presentation at the 2002 American Institute for Cancer Research Conference.

Palomares MR, Richardson-Lander A, LaBrash L, Gralow JR. The effect of phytoestrogens on normal breast tissue in postmenopausal breast cancer survivors: an ongoing trial," poster presentation at the 2002 Department of Defense Era of Hope Meeting.

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Palomares MR, Hopper L, Goldstein L, Lehman CD, Storer BE, Gralow JR. Effect of soy isoflavones on breast proliferation in postmenopausal breast cancer survivors. *Breast Cancer Research and Treatment,* 88 (Supp 1): 4002, 2004.

CONCLUSIONS:

In summary, findings in this small pilot study suggest that isoflavones use by postmenopausal breast cancer survivors probably does not have adverse effects on the normal tissue of the contralateral breast.

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APPENDICES:

1. Palomares MR, Gralow JR. The effect of phytoestrogens on normal breast tissue in postmenopausal breast cancer survivors: a feasibility study," poster presentation at the 2002 American Institute for Cancer Research Conference.

2. Palomares MR, Richardson-Lander A, LaBrash L, Gralow JR. The effect of phytoestrogens on normal breast tissue in postmenopausal breast cancer survivors: an ongoing trial," poster presentation at the 2002 Department of Defense Era of Hope Meeting.

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The Effect of Phytoestrogens on Normal Breast Tissue in Postmenopausal Breast Cancer Survivors: A Feasibility Study

Melanie R. Palomares, M.D. and **Julie R. Gralow, M.D.**
Division of Medical Oncology, Department of Medicine, University of Washington, Seattle, WA

INTRODUCTION

Background

Phytoestrogens have received media attention as a form of breast cancer prevention. Although epidemiologic studies support this claim, there are no prospective clinical trials demonstrating such a protective effect.

Objective

This project, supported by an AICR Postdoctoral Award, is an ongoing randomized clinical trial that aims to evaluate the effect of a phytoestrogen supplement on the breast tissue of postmenopausal breast cancer survivors.

METHODS

Study Design

Sixty disease-free, post-therapy, postmenopausal women with in-situ or early invasive (St. 0-IIA) breast cancer are to be randomized to either 100mg/d isoflavone tablets or placebo for one year. Biopsies of the uninvolved breast are examined for proliferative changes in response to phytoestrogens, as well as immunohistochemical breast cancer biomarkers. Mammography is performed to assess breast density, and for close monitoring for recurrence. As secondary endpoints, menopausal symptoms, vaginal epithelial changes, endometrial histology, and serum steroid hormones are also being measured.

Recruitment Methods

The trial was opened to accrual in June 2001. Initial recruitment was purely clinic based. All returning breast cancer visits at the Seattle Cancer Care Alliance Medical Oncology clinics were screened for the eligibility criteria in Table 1. Patient eligibility was determined in the initial screening via the medical record and then subsequently via patient interview. After the first six months of accrual, community based recruitment was added. Now after the first year of accrual, we compare these two recruitment methods into a chemoprevention trial.

RESULTS

Recruitment

A total of 631 breast cancer patients have been screened through the Seattle Cancer Care Alliance in the first year of accrual. After the first six months, we began community based recruitment and received 56 additional self referrals. From both groups, 467 were found to be ineligible, 52 refused participation, and 14 have consented to participate so far. The number one reason for ineligibility at our institution is stage (76%). Of the women who stated their primary reason for refusal, the most common reasons have been complaints of invasiveness of the trial (15%) and unwillingness to take phytoestrogen supplements (31%).

Follow-up

Of the 10 women actually enrolled in the study, none have reported side effects attributable to the isoflavone tablets. One woman developed a small post biopsy hematoma, and 2 complained of the dressings used, but the others have not complained of significant discomfort with their breast biopsies.

Table 1. Eligibility Criteria

- Age 30 years or more
- Postmenopausal, either naturally, post-oophorectomy, or chemotherapy induced
- Biopsy proven invasive cancer or ductal carcinoma in situ
- Unilateral breast cancer and intact contralateral breast
- Stage 0-II and node negative at diagnosis
- Completed cancer therapy with no residual breast cancer
- No hormonal breast cancer therapy or chemoprevention for at least 3 months
- No systemic hormone replacement therapy or oral contraception for 3 months
- No history of other cancers requiring systemic anticancer treatment within the last 3 months
- No renal insufficiency or hepatic insufficiency
- Able to give informed consent

Table 2. Accrual Summary

TOTAL NUMBER SCREENED	687
PATIENTS COMING TO CLINIC	863
NUMBER SCREENED IN CLINIC	631
NUMBER OF REFERRALS	56
NUMBER OF ELIGIBLE WOMEN	68
RECEIVED INFORMED CONSENT	14
ENROLLED	10

Figure 1A. Outcomes from clinic-based screening (n=631)

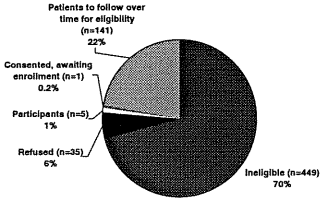


Figure 1B. Outcomes from community-based recruitment (n=56)

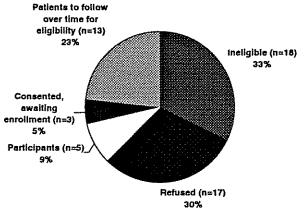


Figure 2A. Reasons for ineligibility for those undergoing clinic-based screening (n=449)

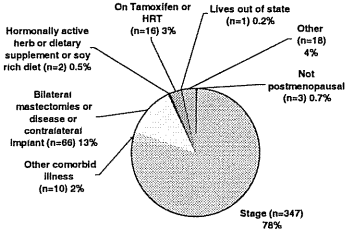
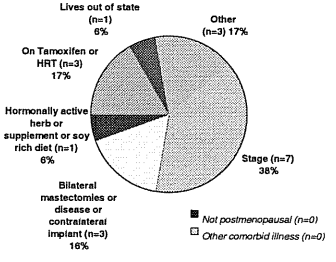


Figure 2B. Reasons for ineligibility for those recruited from community (n=18)



ACKNOWLEDGEMENTS

This study is supported by the Department of Defense Breast Cancer Initiative and Susan G. Komen Breast Cancer Foundation in addition to the AICR. The authors would also like to thank Laurel LaBrash and Annie Richardson-Lander for their work on recruitment and follow-up.

Figure 3A. Reasons for refusal for those undergoing clinic-based screening (n=35)

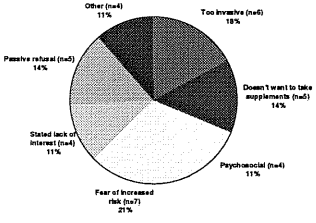
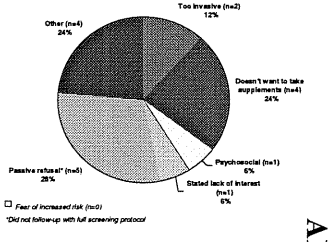


Figure 3B. Reasons for refusal for those recruited from community (n=17)



CONCLUSIONS

- Conduct of a breast chemoprevention trial with histologic endpoints requiring breast biopsy appears feasible. Tissue sampling is acceptable by a subset of women.
- Refusal to take isoflavone tablets is more of a deterrent to participation than the breast biopsy. This was both due to:
  - Fear of stimulation of recurrence, as well as
  - Unwillingness to be randomized to active vs. placebo tablets because of either strong desire for active tablet (unacceptance of placebo control) or preference for a dietary intervention.
- Comparison of clinic and community based recruitment:
  - 41 currently eligible women, and 141 women who are potentially eligible in the near future, have been identified through the clinic. However, 80% of those who are currently eligible have refused participation.
  - On the other hand, while community based recruitment has yielded only 25 eligible women so far (13 are still awaiting review of outside records), those who were eligible were 15 times more likely to participate.
- Isoflavone tablets and breast biopsies are well tolerated by those participating in the trial thus far.

FUTURE DIRECTIONS

- After this analysis, plans are to focus more energy into community based recruitment and expand outreach efforts.
- The investigators have also agreed to relax the stage eligibility criteria to include women with Stage IIB breast cancer, as long as fewer than 4 lymph nodes were involved.
- Mammographic density will be compared to histologic markers.

APPENDIX 1

The Effect of Phytoestrogens on Normal Breast Tissue in Postmenopausal Breast Cancer Survivors: An Ongoing Trial

Melanie R. Palomares, M.D., Annie Richardson-Lander, Laurel LaBrash, and Julie R. Gralow, M.D.

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INTRODUCTION

Background

Phytoestrogens have received media attention as a form of breast cancer prevention. Although epidemiologic studies support this claim, there are no prospective clinical trials demonstrating such a protective effect.

Objective

This project is an ongoing randomized clinical trial that aims to evaluate the effect of a phytoestrogen supplement on the breast tissue of postmenopausal breast cancer survivors. Secondary endpoints include menopausal symptoms and sex steroid hormone levels.

METHODS

Study Design

Sixty disease-free, post-therapy, postmenopausal women with in-situ or early invasive (St. 0-IIA) breast cancer are to be randomized to either 100mg/d isoflavone tablets or placebo for one year. Biopsies of the uninvolved breast are examined for proliferative changes in response to phytoestrogens, as well as immunohistochemical breast cancer biomarkers. Mammography is performed to assess breast density, and for close monitoring for recurrence. As secondary endpoints, menopausal symptoms, vaginal epithelial changes, endometrial histology, and serum steroid hormones are also being measured.

Recruitment Methods

The trial was opened to accrual in June 2001. Initial recruitment was purely clinic based. All returning breast cancer visits at the Seattle Cancer Care Alliance Medical Oncology clinics were screened for the eligibility criteria in Table 1. Patient eligibility was determined in the initial screening via the medical record and then subsequently via patient interview. After the first six months of accrual, community based recruitment was added. Now after the 18 months of accrual, we compare these two recruitment methods in this chemoprevention trial.

RESULTS

Recruitment

A total of 801 breast cancer patients have been screened through the Seattle Cancer Care Alliance in the first year of accrual. After the first six months, we began community based recruitment and received 62 additional self referrals. From both groups, 577 were found to be ineligible, 76 refused participation, and 18 have consented to participate so far. The number one reason for ineligibility is stage (58%). Of the women who stated their primary reason for refusal, the most common reasons have been complaints of invasiveness of the trial (12%) and unwillingness to take phytoestrogen supplements (30%).

Follow-up

Of the 16 women enrolled in the study, none have reported side effects attributable to the isoflavone tablets. One woman developed a small post biopsy hematoma, and 2 complained of the dressings used, but the others have not complained of significant discomfort with their breast biopsies.

Table 1. Eligibility Criteria

- Age 30 years or more
- Postmenopausal, either naturally, post-oophorectomy, or chemotherapy induced
- Biopsy proven invasive cancer or ductal carcinoma in situ
- Unilateral breast cancer and intact contralateral breast
- Stage 0-II and node negative at diagnosis
- Completed cancer therapy with no residual breast cancer
- No hormonal breast cancer therapy or chemoprevention for at least 3 months
- No systemic hormone replacement therapy or oral contraception for 3 months
- No history of other cancers requiring systemic anticancer treatment within the last 3 months
- No renal insufficiency or hepatic insufficiency
- Able to give informed consent

Table 2. Accrual Summary

TOTAL NUMBER SCREENED	863
PATIENTS COMING TO CLINIC	1511
NUMBER SCREENED IN CLINIC	801
NUMBER OF REFERRALS	62
NUMBER OF ELIGIBLE WOMEN	100
RECEIVED INFORMED CONSENT	18
ENROLLED	16

Figure 1A. Outcomes from clinic-based screening (n=801)

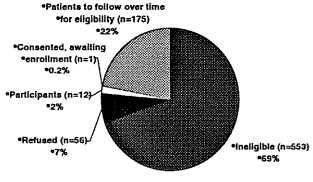


Figure 1B. Outcomes from community-based recruitment (n=62)

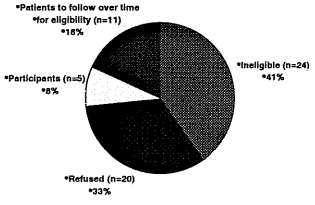


Figure 2A. Reasons for ineligibility for those undergoing clinic-based screening (n=553)

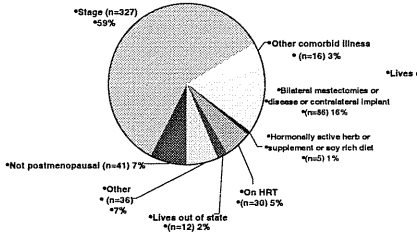
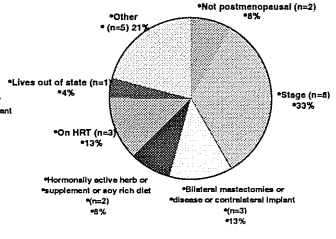


Figure 2B. Reasons for ineligibility for those recruited from community (n=24)



ACKNOWLEDGEMENTS

This study is supported by the Department of Defense Breast Cancer Research Program, DAMD 17-01-1-0449.

Figure 3A. Reasons for refusal for those undergoing clinic-based screening (n=35)

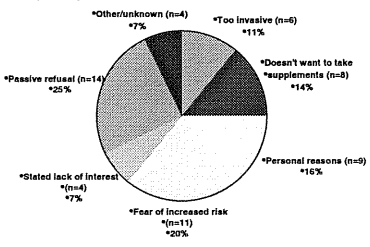
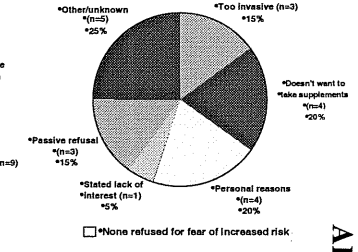


Figure 3B. Reasons for refusal for those recruited from community (n=17)



CONCLUSIONS

- Conduct of a breast chemoprevention trial with histologic endpoints requiring breast biopsy appears feasible. Tissue sampling is acceptable by a subset of women.
- Refusal to take isoflavone tablets was 2.5 times more of a deterrent to participation than the breast biopsy. This was both due to:
  - Fear of stimulation of recurrence, as well as
  - Unwillingness to be randomized to active vs. placebo tablets because of either strong desire for active tablet (unacceptance of placebo control) or preference for a dietary intervention.
- Both isoflavone tablets and breast biopsies are well tolerated by those participating in the trial thus far.
- Comparison of clinic and community based recruitment: Women who self-referred were 5 times more likely to participate than those who were screened through the clinic.

FUTURE DIRECTIONS

- After this analysis, plans are to focus more energy into community based recruitment and expand outreach efforts.
- The investigators have also agreed to relax the stage eligibility criteria to include women with Stage IIB breast cancer, as long as fewer than 4 lymph nodes were involved.

APPENDIX 2

APPENDIX 3

Feasibility of Breast Tissue Sampling in a Chemoprevention Trial with Histologic Biomarker Endpoints

Melanie R. Palomares, MD, MS; Lynn Goldstein, MD; Constance D. Lehman, MD, PhD; Laura Hopper; Julie R. Gralow, MD

University of Washington, Seattle WA; Phenopath Laboratories, Seattle WA

Background: Phytoestrogens are natural selective estrogen receptor modulators (SERMs) found in soy foods that show effects similar to endogenous estrogens. Epidemiologic studies have shown an association between high soy consumption and a decreased risk of developing breast cancer. Prospective human trials have been few and small, and have reported contradictory results. The purpose of this study is to assess the effect of taking a phytoestrogen dietary supplement for one year on breast epithelial proliferative activity, in a placebo-controlled randomized clinical trial.

Methods: Twenty-two disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer were randomized to receive either 100mg per day isoflavone tablets, or placebo for 12 months. Ultrasound-guided 14-gauge core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. Histological sections are evaluated for breast epithelial proliferation by Ki-67 index. All subjects had a documented normal screening mammogram and clinical breast exam prior to each biopsy.

Results: Of the 22 subjects enrolled, 21 have available baseline pathology results. Eight subjects have completed the 12-month trial. Full biopsy series are available on 7 of those subjects. An additional 4 subjects have completed both baseline and 6-month biopsies and therefore have one comparison available. Of all 64 biopsies performed, all but one baseline and one follow-up had sufficient tissue yield from our ultrasound-guided biopsy method in order to assess epithelial histology and Ki-67 index, as well as mitotic index and ER/PR expression (97% successful yield). Although the trial is still blinded, results have been quite interesting thus far. Despite the fact that tissue sampling was from the contralateral breast, and all participants were postmenopausal, 10 of 21 baseline biopsies revealed hyperplasia. Two of those had atypical hyperplasia evident on their random biopsy; the other eight had usual hyperplasia. Immunohistochemistry results are available on 18 of the 21 baseline biopsies, and average Ki67 index was 9.2%. We would expect this to be <5% in a normal-risk postmenopausal population. All subjects had zero mitotic index at baseline. All expressed hormone receptors at baseline.

Conclusions: Recruitment into a chemoprevention trial with histological biomarker endpoints requiring serial breast biopsies is feasible, at least within the breast cancer survivor population. Obtaining adequate breast epithelial tissue from postmenopausal women for evaluation of histology and multiple immunohistochemical markers is possible >90% of the time using ultrasound-guided 14-gauge core biopsy. Pathologic examination of the sampled contralateral breast epithelia reveals more proliferative activity than would be expected in a similarly aged unaffected population.

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1034 Feasibility of Breast Tissue Sampling in a Chemoprevention Trial with Histologic Biomarker Endpoints

Melanie R. Palomares, MD, MS;[1,2] Lynn Goldstein, MD;[3] Constance D. Lehman, MD, PhD;[2] Laura Hopper;[2] Julie R. Gralow, MD.[2]
[1]City of Hope National Medical Center, Duarte, CA; [2]University of Washington School of Medicine, Seattle, WA; [3]PhenoPath Laboratories, Seattle, WA

INTRODUCTION

Background

Phytoestrogens are natural selective estrogen receptor modulators (SERMs) found in soy foods that show effects similar to endogenous estrogens. Epidemiologic studies have shown an association between high soy consumption and a decreased risk of developing breast cancer. Prospective human trials have been few and small, and have reported contradictory results.

Objective

The purpose of this study is to assess the effect of taking a phytoestrogen dietary supplement for one year on breast epithelial proliferative activity, in a placebo-controlled randomized clinical trial.

METHODS

Study Population

Twenty-two disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage I-II) breast cancer were recruited through the medical oncology clinics at the Seattle Cancer Care Alliance between July 2001 and March 2003 into the UW Phytoestrogen Trial. Subjects were randomized to receive either 100mg per day isoflavone tablets, or placebo for 12 months. Study follow-up is ongoing, and subjects remain blinded at this time. We report our feasibility experience with breast tissue sampling and preliminary histologic findings.

Tissue Collection and Processing

All subjects had a documented normal screening mammogram and clinical breast exam prior to each biopsy. Ultrasound-guided 14-gauge core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. Histological sections are evaluated for breast epithelial proliferation by Ki-67 index and hormone receptor expression.

ACKNOWLEDGEMENTS

Support for this study is being provided by the Department of Defense, DAMD17-01-1-0449

RESULTS

Figure 1: UW Phytoestrogen Trial schema

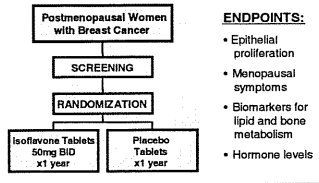


Table 1: Patient population

Inclusion criteria

1 – Postmenopausal women age 30 or older
2 - Unilateral Stage I-II infiltrating ductal or infiltrating lobular carcinoma, or ductal carcinoma in-situ (DCIS)
3 - Completed appropriate local and adjuvant systemic therapy with no evidence of residual disease

Exclusion criteria

1 – 4+ lymph node involvement
2 – S/P bilateral mastectomy
3 – contralateral breast implant
4 – Estrogen-modulating therapy, including SERM, aromatase inhibitor, HRT, or hormonally-active herbal supplement, within 3 months of enrollment
5 – Baseline soy-rich diet, defined as more than 3 servings per week (average 10mg isoflavones per day)

Table 2: Patient characteristics

N	22	
Mean age	57.0	years
Mean time since diagnosis	5.4	years
Stage distribution:		
0	2	9%
I	10	45%
II	10	45%
ER status:		
positive	13	59%
negative	6	27%
unknown	3	14%

Figure 2: Guided biopsy technique

Mammography of the contralateral breast was first obtained to determine background mammographic density. Ultrasound then was used to identify a location within the contralateral breast with fibroglandular density. Five 14-gauge core biopsies were obtained through a single skin entry.

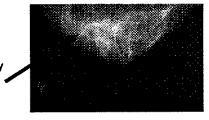


Table 3: Biopsy yield

	Visit			
	Baseline	6 month	12 month	Total
Adequate**	21 (95.5%)	17 (94.4%)	12 (100.0%)	50 (96.2%)
Insufficient	1 (4.5%)	1 (5.6%)	0 (0.0%)	2 (3.8%)
Total Obtained	22	18	12	52

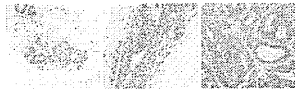
**refers to adequate glandular tissue for assessment of histology, Ki-67 index, and ER/PR expression.

Table 4: Baseline histologic results

N with baseline path available	21		
Histology:			
Normal	11	52%	
Hyperplasia without atypia	8	38%	
Hyperplasia with atypia	2	10%	
Mean Ki67 index*	8.5%	range: 1-30%	
ER expression:			
none	0	0%	
1+	0	0%	
2+	9	43%	
3+	12	57%	
PR expression:			
none	0	0%	
1+	6	29%	
2+	10	48%	
3+	5	24%	

Figure 3: Histological classification

Each biopsy is read by a single study pathologist.



Normal glandular tissue | Usual hyperplasia | Atypical hyperplasia

*Figure 4: Ki-67 index

is expressed as the ratio of stain-positive cells per 100 cells counted

Figure 5: ER/PR expression

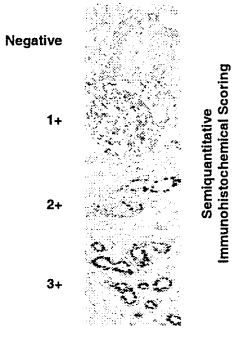


Table 5. Preliminary histologic follow-up

	6 months	12 months
N:	16	10
Histology:		
Normal	10	6
Hyperplasia without atypia	5	4
Hyperplasia with atypia	1	0
Ki67 index*:		
Mean	7.5%	7.6%
Range	0-20%	1-19%
ER expression:		
none	0	0
1+	0	1 (6%)
2+	5 (31%)	4 (25%)
3+	11 (69%)	5 (31%)
PR expression:		
none	0	0
1+	1 (6%)	3 (19%)
2+	12 (75%)	5 (31%)
3+	3 (19%)	2 (13%)

CONCLUSIONS

- **Recruitment into a chemoprevention trial with histological biomarker endpoints requiring serial breast biopsies is feasible, at least within the breast cancer survivor population.**
- **Obtaining adequate breast epithelial tissue from postmenopausal women for evaluation of histology and multiple immunohistochemical markers is possible >95% of the time using ultrasound-guided 14-gauge core biopsy.**
- **Pathologic examination of the sampled contralateral breast epithelia reveals more proliferative activity than would be expected in a similarly aged unaffected population.**
- **All normal breast tissue sampled expressed hormone receptors.**
- **Preliminary follow-up suggests a possible decrease in Ki-67 index and estrogen receptor expression with isoflavone treatment; however, whether that trend is significantly different to placebo remains to be seen.**

APPENDIX 3

APPENDIX 4

Acceptability of breast core biopsy as a tissue sampling method for a chemoprevention trial

Melanie R. Palomares, MD, MS; Laura Hopper; Lynn Goldstein, MD;
Constance D. Lehman, MD, PhD; Julie R. Gralow, MD

City of Hope, Duarte, CA; University of Washington, Seattle WA;
Phenopath Laboratories, Seattle WA

Background: Early phase chemoprevention clinical trials often require histologic biomarker endpoints. Current options for breast tissue collection to evaluate such markers include nipple aspirate, ductal lavage, periareolar fine needle aspirate, and core needle biopsy. Trade-offs between methods include degree of invasiveness and adequate tissue yield. Core needle biopsy is the most invasive method, but has the benefits of greater epithelial cell yield and preserved glandular architecture. We report yield and acceptability of core biopsy in a trial assessing the effect of a phytoestrogen dietary supplement on breast epithelial proliferative activity.

Methods: Twenty-two disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer were randomized to receive either 100mg per day isoflavone tablets, or placebo for 12 months. Ultrasound-guided 14g core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. Histological sections were evaluated for breast epithelial proliferation by Ki-67 index. Questionnaires evaluating pain, anxiety, and quality of life (QOL) were collected one week post biopsy.

Results: Of 52 biopsies performed in 22 subjects, all but one baseline and one follow-up had sufficient tissue yield to assess epithelial histology and Ki-67 index, as well as mitotic index and ER/PR expression (96% successful yield). Of the 48 for whom questionnaire data are available, 17 (35%) reported no pain associated with breast biopsy. Of the remaining 31 reporting any post biopsy pain, on a scale of 1-10, their average pain score was 1.5 +/- 1.1. Twelve (39%) did not require any pain medications to alleviate their pain. Those who did typically used over-the-counter acetominophen or ibuprofen, from which they experienced on average 74% relief. Twenty-three (74%) reported that their pain had completed abated within two days. Sixteen (38%) reported no anxiety associated with breast biopsy. The remaining 32 reporting any biopsy-associated anxiety on average rated their anxiety 1.8 +/- 1.5 prebiopsy and 1.7 +/- 1.6 post-biopsy. Regarding how pain and/or anxiety affected QOL, 67% reported no effect on level of activity (mean score 0.64 +/- 1.1), 81% reported no effect on their relationships with others (0.12 +/- 0.42), 79% reported no effect on their sleep (0.36 +/- 0.9), and 64% reported no effect on their mood (0.76 +/- 1.3).

Conclusions: Ultrasound guided 14g core breast biopsy yields adequate breast epithelial tissue from postmenopausal women for evaluation of multiple immunohistochemical markers >90% of the time, and is well tolerated with respect to pain, anxiety, and QOL.

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1344 Acceptability of Breast Core Biopsy as a Tissue Sampling Method for a Chemoprevention Trial

Melanie R. Palomares, MD, MS;[1,2] Laura Hopper;[2] Lynn Goldstein, MD;[3] Constance D. Lehman, MD, PhD;[2] Julie R. Gralow, MD.[2]
[1]City of Hope National Medical Center, Duarte, CA; [2]University of Washington School of Medicine, Seattle, WA; [3]PhenoPath Laboratories, Seattle, WA

INTRODUCTION

Background

Early phase chemoprevention clinical trials often require histologic biomarker endpoints. Current options for breast tissue collection to evaluate such markers include nipple aspirate, ductal lavage, periareolar fine needle aspirate, and core needle biopsy. Trade-offs between methods include degree of invasiveness and adequate tissue yield. Core biopsy is the most invasive method, but has the benefits of greater epithelial cell yield and preserved glandular architecture.

METHODS

Study Population

Twenty-two disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage I-II) breast cancer were recruited through the medical oncology clinics at the Seattle Cancer Care Alliance between July 2001 and March 2003 into the UW Phytoestrogen Trial. Subjects were randomized to receive either 100mg per day isoflavone tablets, or placebo for 12 months. Study follow-up is ongoing, and subjects remain blinded at this time. We report our feasibility and acceptability data with breast tissue sampling using core biopsy.

Tissue Collection and Processing

All subjects had a documented normal screening mammogram and clinical breast exam prior to each biopsy. Ultrasound-guided 14-gauge core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. A specimen was considered adequate when it included enough glandular tissue for assessment of histology, Ki-67 index, and ER/PR expression.

Symptom Data Collection

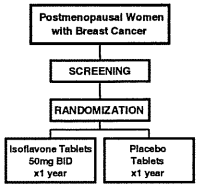
Subjects were given symptom logs on which they rated their anxiety and pain levels on a scale of 1-10. Anxiety was rated immediately prior to the procedure and one week post procedure. Worst and least pain levels experienced during the week following the procedure were rated, and information regarding pain duration and medication was also collected. To provide comparison data, subjects were given the same symptom log to rate anxiety and pain associated with mammography.

ACKNOWLEDGEMENTS

Support for this study is provided by the Department of Defense, DAMD17-01-1-0449

RESULTS

UW Phytoestrogen Trial Schema



ENDPOINTS:

- Epithelial proliferation
- Menopausal symptoms
- Biomarkers for lipid and bone metabolism
- Hormone levels

Study population

Inclusion criteria

1 – Postmenopausal women age 30 or older
2 – Unilateral Stage I-II infiltrating ductal or infiltrating lobular carcinoma, or ductal carcinoma in-situ (DCIS)
3 – Completed appropriate local and adjuvant systemic therapy with no evidence of residual disease

Exclusion criteria

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5 – Baseline soy-rich diet, defined as more than 3 servings per week (average 10mg isoflavones per day)

Patient characteristics

N	22	
Mean age	57.0	years
Mean time since diagnosis	5.4	years
Stage distribution:		
0	2	9%
I	10	45%
II	10	45%
ER status:		
positive	13	59%
negative	6	27%
unknown	3	14%

Biopsy yield

	Visit			
	Baseline	6 month	12 month	Total
Adequate	21 (95.5%)	17 (94.4%)	12 (100.0%)	50 (96.2%)
Insufficient	1 (4.5%)	1 (5.6%)	0 (0.0%)	2 (3.8%)
Total Obtained	22	18	12	52

Biopsy-Associated Pain*

17 of 48 symptom logs (35%) reported no pain associated with breast biopsy.

The remaining 31 reported the following mean worst, least, and average pain scores:

Worst pain	**2.5 +/- 1.5**
Least pain	**0.5 +/- 0.9**
Average pain	**1.5 +/- 1.1**

12 of the 31 (39%) did not require any pain medications to alleviate their pain. Those who did typically used over-the-counter acetominophen or ibuprofen, from which they experienced on average 74% pain relief.

23 of the 31 (74%) subjects reporting any post-biopsy pain said that their pain had completely abated within two days.

Biopsy-Associated Anxiety*

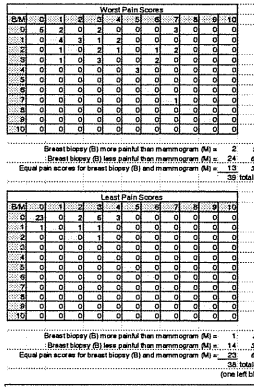
16 of 48 symptom logs (33%) reported no anxiety associated with breast biopsy.

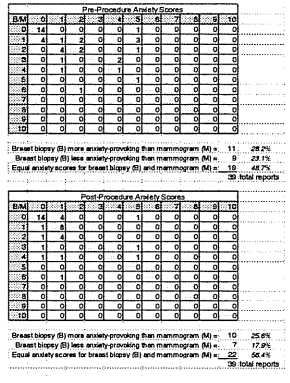
The remaining 32 reported the following mean pre, post, and average anxiety scores:

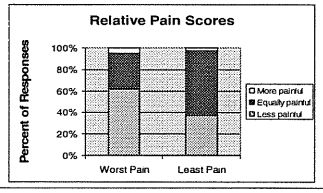
Pre-procedure	**1.8 +/- 1.5**
Post-procedure	**1.7 +/- 1.6**
Average	**1.7 +/- 1.0**

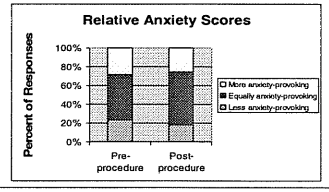
There was no significant change between pre- and post-procedure anxiety.

Pain and Anxiety Relative to Mammography*









*Out of the 52 biopsies collected, symptom log data is available for 48. Comparison mammogram symptom logs are available for 39.

CONCLUSIONS

- **Breast core biopsy is a well-tolerated procedure that yields adequate tissue for multiple histological biomarkers for chemoprevention:**
- **Obtaining adequate breast epithelial tissue from postmenopausal women for evaluation of histology and multiple immunohistochemical markers is possible ≥95% of the time using ultrasound-guided 14-gauge core biopsy.**
- **Breast core biopsy was not associated with pain in one-third of cases, and was associated with only low levels of self-limited pain in the remaining cases.**
- **Breast core biopsy was not associated with anxiety in one-third of cases, and was associated with only low levels of pre- and post-procedure anxiety in the remaining cases.**
- **The pain and anxiety associated with breast core biopsy was less than or equal to that experienced with mammogram in ≥95% and ≥75% of cases, respectively.**

APPENDIX 4

APPENDIX 5

Effect of Phytoestrogens on Menopausal Symptoms in Breast Cancer Survivors

Melanie R. Palomares, MD, MS; Laura Hopper; Johanna W. Lampe, PhD;
Barry E. Storer, PhD; Julie R. Gralow, MD

City of Hope Comprehensive Cancer Center, Duarte, CA; Seattle Cancer Care Alliance, Seattle WA;
Fred Hutchinson Cancer Research Center, Seattle, WA

Introduction: Most women with breast cancer are postmenopausal at diagnosis, and many more enter menopause during the course of their treatment. The majority of these women will be long-term survivors who must manage their menopausal symptoms without the option of hormone replacement. Studies suggest that soy supplements may be used as an alternative, but most of those studies were not conducted in breast cancer survivors. One study investigated a four-week course of a soy isoflavone supplement in women with breast cancer and found no benefit with respect to vasomotor symptoms. However, two-thirds of the participants were taking tamoxifen at the same time.

Purpose: To evaluate the effect of a year-long trial of soy isoflavone supplementation on menopausal symptoms in breast cancer survivors who have completed all cancer treatment, including hormonal therapy.

Methods: Postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer who were disease-free post-therapy were randomized to receive tablets providing either soy isoflavones (100 mg aglycone units/day), or placebo, for 12 months. Menopausal symptom logs were collected from all participants at baseline, and after 3, 6, 9, and 12 months on the study supplement.

Results: Twenty-three subjects enrolled in the trial, with a median age of 57 (range 45-67). Seventeen (74%) had hormone receptor expressing tumors and had previously taken antiestrogen therapy, but they were a median of 5.9 years post-diagnosis (range 1.2-12.9), and no one was taking any hormonal therapy for at least 3 months prior to enrollment. All but one participant had menopausal symptoms at baseline. A full year of follow-up is available for 16 subjects; average overall follow-up is 9.8 months. Pill counts reveal high adherence to treatment plan (≥90%), and urinary isoflavones were significantly elevated in the treatment group (p=0.0001). On average, participants in both treatment groups experienced a decline in the number and severity of hot flashes from baseline. As depicted in the accompanying graphs, there was a slightly greater decrease in the number of hot flashes between 3 and 9 months of isoflavone treatment relative to placebo, but by 12 months the placebo group had experienced similar relief in hot flashes. The decrease in severity of hot flashes with isoflavones was most pronounced at 3 and 6 months, but a trend remained throughout the treatment period. There were no significant differences in the genitourinary symptoms of vaginal dryness, incontinence, dyspareunia, and libido between the treatment groups, although there was a trend toward improvement in incontinence and libido with isoflavone supplementation (see graphs below). Vaginal discharge and dysuria were too infrequently reported at baseline to analyze.

Conclusions: Preliminary results from this pilot trial suggest that soy supplements may be effective at decreasing the number and severity of hot flashes in postmenopausal breast cancer survivors in the short-term, but that all women experience relief over time. Similarly, no significant changes in genitourinary symptoms were observed in this small study sample, but some beneficial trends were observed with isoflavone supplementation compared to placebo.

Society of Integrative Oncology, Nov 17-19 NYC
http://www.integrativeonc.org/index.php?scn=meeting_program

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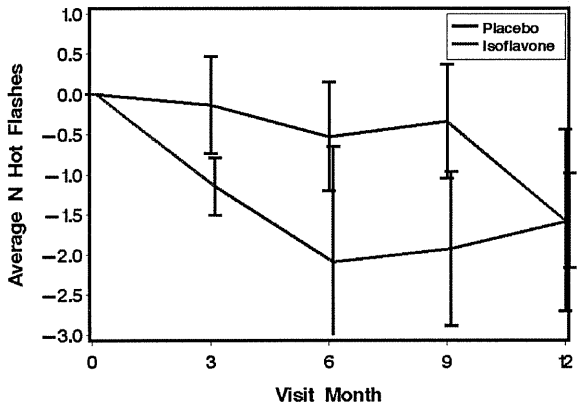

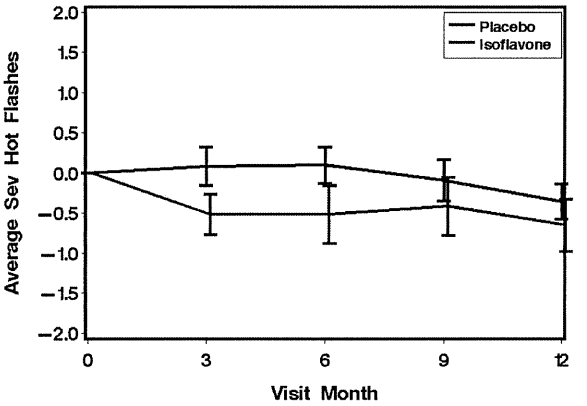

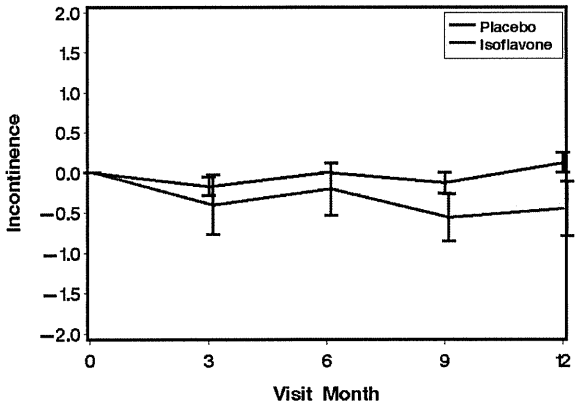

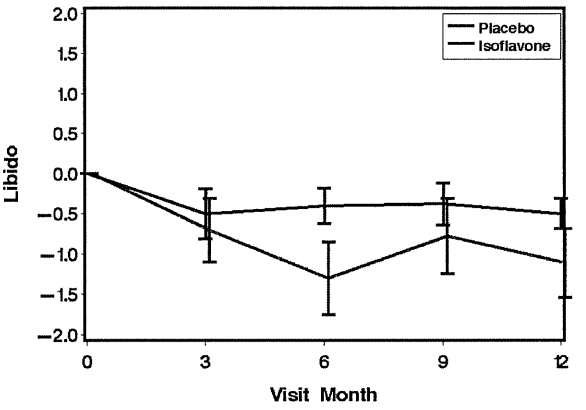

Effect of Soy Isoflavones on Breast Proliferation in Postmenopausal Breast Cancer Survivors

Melanie R. Palomares, MD, MS; Laura Hopper; Lynn Goldstein, MD;
Constance D. Lehman, MD, PhD; Johanna W. Lampe, PhD;
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Phenopath Laboratories, Seattle WA; University of Washington, Seattle, WA;
Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Most women with breast cancer are postmenopausal at diagnosis, and many more enter menopause during the course of their treatment. The majority of these women will be long-term survivors who must manage their menopausal symptoms without the option of hormone replacement. Some use soy supplements as an alternative, but preclinical studies have shown both stimulatory and inhibitory effects of soy isoflavones on the breast. We report initial results from a pilot human clinical trial assessing the effect of a soy supplement on breast epithelial proliferative activity.

Methods: Postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer who were disease-free after completing all cancer therapy were randomized to receive either 100mg per day isoflavone tablets, or placebo for 12 months. Ultrasound-guided 14g core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. Histological sections were evaluated for breast epithelial proliferation by Ki-67 index.

Results: Twenty-three subjects enrolled in the trial, with a median age of 57 (range 45-67) and median time since diagnosis of 5.9 years (range 1.2-12.9). Mean baseline Ki67 index was 8.1% (range 0-30%), while that expected in the postmenopausal normal breast is <5%. At 6 months of follow-up, pill counts reveal high adherence to the treatment plan (≥90%), and urinary isoflavones were significantly higher in the treatment group (p=0.0001). Evaluable pre and post-treatment histological specimen pairs are available for 18 subjects (9 in each arm). On average, Ki67 index dropped during 6 months of treatment for both groups: a 3.1% (SD 9.5%) decrease was noted in the isoflavone group, while a 1.3% (SD 8.5%) decrease from baseline was observed in the placebo group. This difference was not statistically significant.

Conclusions: Preliminary results from this pilot trial suggest that soy supplements do not increase proliferation of normal breast tissue in breast cancer survivors. The elevated mean Ki67 index observed at baseline correlates with the known increased risk for contralateral breast cancer in this population.

San Antonio Breast Cancer Symposium, Dec 8-11
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Johanna W. Lampe, PhD;[3] Barry E. Storer, PhD;[3] and Julie R. Gralow, MD.[2]
[1]City of Hope National Medical Center, Duarte, CA; [2]University of Washington School of Medicine, Seattle, WA;
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BACKGROUND

Most women with breast cancer are postmenopausal at diagnosis, and many more enter menopause during the course of their treatment. The majority will be long-term survivors who must manage their menopausal symptoms without the option of hormone replacement therapy (HRT). Some women use soy supplements as an alternative to HRT, but preclinical studies have shown both stimulatory and inhibitory effects of soy isoflavones on the breast. We report results from a pilot human clinical trial assessing the effect of a soy supplement on breast epithelial proliferative activity.

METHODS

Study Population

Twenty-three disease-free, post-therapy, postmenopausal women previously diagnosed with in-situ or early stage invasive (Stage I-II) breast cancer were recruited through the medical oncology clinics at the Seattle Cancer Care Alliance (SCCA) between July 2001 and March 2003 into the University of Washington (UW) Phytoestrogen Trial. Subjects were randomized to receive either 100mg per day isoflavone tablets (ISO), or placebo (PBO) for 12 months. Compliance was measured by both pill counts and 24-hour urinary genistein levels. Follow-up was completed in May 2004.

Tissue Sampling and Processing

Ultrasound-guided 14-gauge core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. All subjects had a documented normal screening mammogram and clinical breast exam prior to each biopsy. A specimen was considered adequate when it included enough glandular tissue for assessment of histology, Ki-67 index, and ER/PR expression. A subject was considered evaluable if both baseline and at least one of the follow-up breast biopsy specimens were adequate.

ACKNOWLEDGEMENTS

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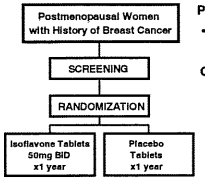
RESULTS

1. UW/SCCA Phytoestrogen Trial Schema



PRIMARY ENDPOINT

- Epithelial proliferation (Ki-67 Index)

OTHER ENDPOINTS

- Menopausal symptoms
- Biomarkers for lipid and bone metabolism
- Hormone levels

2. Study Population

Inclusion criteria

1 – Postmenopausal women age 30 or older
2 – History of unilateral Stage I-II infiltrating ductal or infiltrating lobular carcinoma, or ductal carcinoma in-situ (DCIS)
3 – Completed appropriate local and adjuvant systemic therapy with no evidence of residual disease

Exclusion criteria

1 – 4+ lymph node involvement
2 – S/P bilateral mastectomy
3 – Contralateral breast implant
4 – Estrogen-modulating therapy, including SERM, aromatase inhibitor, HRT, or hormonally-active herbal supplement, within 3 months of enrollment
5 – Baseline soy-rich diet, defined as more than 3 servings per week (average 10mg isoflavones per day)

3. Patient Tumor Characteristics

	Total		ISO		PBO		p-value
N	23		11		12		
	Mean	SD	Mean	SD	Mean	SD	
Age	56.9	1.4	56.5	2.1	57.3	2.0	NS
Years since diagnosis	5.9	0.7	4.2	0.8	7.6	0.9	<0.01
Histology:	N	%	N	%	N	%	
DCIS	3	13%	2	18%	1	8%	NS
IDC	17	74%	7	64%	10	83%	
ILC	3	13%	2	18%	1	8%	
Stage at diagnosis:	N	%	N	%	N	%	
0	2	9%	1	9%	1	8%	NS
I	11	48%	4	36%	7	58%	
II	10	43%	6	55%	4	33%	
Grade at diagnosis:	N	%	N	%	N	%	
low	5	22%	4	36%	1	8%	NS
intermediate	8	35%	0	0%	8	67%	
high	7	30%	7	64%	0	0%	
unknown	3	13%	0	0%	3	25%	
Receptor status:	N	%	N	%	N	%	
ER/PR +	17	74%	6	55%	11	92%	0.05

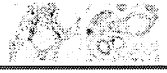
4. Baseline Breast Biopsy Findings

N:	23	
Histology:		
Normal	12	52%
Hyperplasia without atypia	8	35%
Hyperplasia with atypia	2	9%
Inadequate sample	1	4%
Mean Ki67 index* (n=22):	8.1%	range: 0-30%
ER expression:		
1+:	0	0%
2+:	9	39%
3+:	12	52%
not available:	2	9%
PR expression:		
1+:	6	26%
2+:	10	43%
3+:	5	22%
not available:	2	9%

There were no significant differences between treatment assignment groups for any of the characteristics listed.

*Ki-67 Index

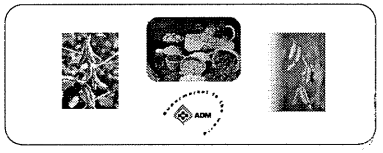
- Primary measure of epithelial proliferation
- Expressed as the ratio of stain-positive cells per 100 cells



5. Treatment Adherence

	ISO	PBO	Difference	p-value
By pill count** (% pills dispensed)				
Baseline	–	–		
6 months	93%	87%	6%	NS
12 months	97%	90%	7%	NS
By urinary genistein (μmol/d)				
Baseline	1.8	1.4	0.4	NS
6 months	19.3***	0.9	18.4	< 0.0001
12 months	14.2***	0.1	14.1	< 0.005

**symptom logs revealed no adverse side effects associated with treatment
***significantly changed from baseline ($p \leq 0.001$)



6. Serial Breast Biopsy Findings

21 subjects completed the study with 11.7 months average follow-up. 19 (90%) of those subjects were evaluable (baseline and follow-up biopsies were adequate).

After 6 months of treatment:

	ISO	PBO		ISO	PBO
N:	9	10	ER expression:		
			negative	0	0
Histology:			1+	0	0
Normal	4	6	2+	2	4
Hyperplasia without atypia	4	2	3+	6	6
Hyperplasia with atypia	0	1	indeterminate	1	0
Benign fibrocystic change	0	1			
Inadequate	1	0	PR expression:		
			negative	0	0
Ki67 index*:			1+	0	1
Mean	6.1%	7.4%	2+	6	8
SD	5.0%	7.8%	3+	2	1
			indeterminate	1	0

After 12 months of treatment:

	ISO	PBO		ISO	PBO
N:	9	9	ER expression:		
			negative	0	0
Histology:			1+	2	0
Normal	5	5	2+	2	6
Hyperplasia without atypia	2	2	3+	3	2
Hyperplasia with atypia	0	1	indeterminate	2	1
Benign fibrocystic change	0	0			
Inadequate	2	1	PR expression:		
			negative	0	0
Ki67 index*:			1+	2	1
Mean	5.4%	5.9%	2+	5	5
SD	6.5%	5.2%	3+	0	2
			indeterminate	2	1

CONCLUSIONS

- A year-long treatment with a twice daily isoflavone tablet was well tolerated by postmenopausal breast cancer survivors. Isoflavone treatment was associated with a 7-10 fold increase in urinary excretion of genistein ($p < 0.005$), with no increase in urinary genistein levels observed in the placebo group.
- Obtaining adequate normal breast epithelial tissue from postmenopausal women for evaluation of multiple serial immunohistochemical biomarkers is possible 90% of the time using ultrasound-guided 14-gauge core biopsy.
- Ki67 index was elevated at baseline, correlating with the known increased risk for contralateral breast cancer in this population. On average, Ki67 index dropped during the first 6 months of treatment: a 3.1% (SD 9.5%) decrease from baseline was noted in the isoflavone group, while a 0.9% (SD 8.1%) decrease was observed in the placebo group. This difference was not statistically significant. During the second 6 months of treatment, Ki67 index continued to decrease in both groups: a 4.9% (SD 11.5%) decrease from baseline was observed in the isoflavone group, and a similar 4.1% (SD 9.0%) decrease was seen with placebo.
- Hyperplasia was observed in 44% of subjects at baseline; however, there were no significant differences found on serial histology between the treatment groups .
- No significant differences between the treatment groups were seen with regards to hormone receptor expression. A trend toward decreased ER expression was noted in both the isoflavone and placebo treated groups over time.

In summary, findings in this small pilot study suggest that isoflavone use by postmenopausal breast cancer survivors probably does not have adverse effects on the normal tissue of the contralateral breast.

APPENDIX 6